INI - Summary

Summary of Matthew's Lectures (3/3)

I. What is an artificial neural network (ANN)?

- It is a computational model that is inspired by the way biological neurons perform computation.
- Their power comes from the different problem-solving paradigm in which they express:
  - In typical "programming" problems, one has to have an almost complete understanding of the problem in order to come up with a formulated solution.
  - In the case of ANNs, a minimum understanding of the problem is required since you can use training data (which is often readily available) to "teach" your network by example, much like a child learns how to identify a dog by first seeing many different patterns of dogs.
- We could use ANNs to model a variety of things: from weather forecasting to the prediction of agricultural and financial systems!

II. Types of Learning:

- supervised
- Supervised Learning: that involves an external teacher. Each output unit is told what the desired response to the input should be. This is what will be talking about. An important point that arises with this type of learning is the error convergence problem: determining the set of weights that reduces the error between the actual output we get from the network and the desired output. We specifically talk about the error back propagation algorithm as one technique of this.
- unsupervised
- Unsupervised Learning: requires no external teacher, and is based on local information only.

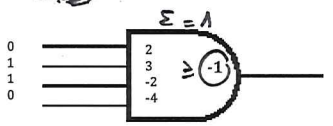
III. McCulloch-Pitt's Model:

- This is a **model** of computing elements that performs a weighted sum of their inputs followed by a threshold logic operation.
- Model neurons as a transistor/switch ~= 2 states: 0/1 = OFF/ON = digital representation. This is an oversimplification.
- The weight: a simple abstraction for the complexity of the synapse.
- Convention for the weights:
  - +ve = excitatory.
  - -ve = inhibitory.
  - How is this consistent with what we established b4 regarding synapses (in Rodney's lectures)? Well, we said that a synapse is considered excitatory if the Nernst potential (reversal potential) is more depolarized (less negative) than the resting potential. The opposite is true for an inhibitory synapse in which case the reversal potential is more negative than the resting potential. With that said, if we define the weight as: $W \sim= V_{Reversal} - V_{Resting}$ then when the reversal potential is more negative than the resting potential, we end up with a negative value for W, and thus we conclude that this is an inhibitory synapse, which is consistent with what we've said before.

↑ depol = excit

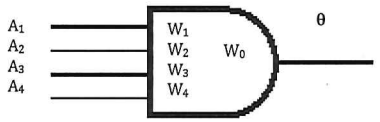
Likewise, if $V_{Revesal}$ is more depolarized than $V_{Resting}$, then the value of W would be positive indicating that it is an excitatory synapse. This means that our convention for taking a $+W$ to indicate an excitatory synapse and a $-W$ to indicate an inhibitory synapse is well justified.

- The red *-1* indicates the threshold the membrane voltage needs to cross in order to create a spike.



- So in general a McCulloch-Pitt's neuron would look like this:

Mc Culloch-Pitt



- And the equation governing its behavior would be:

$$\theta = A_1W_1 + A_2W_2 + A_3W_3 + A_4W_4 + W_0$$

θ = a · w

$$\theta = A \cdot W + W_0$$

$$\theta(x) = \begin{cases} 0 & if\ x < 0 \\ 1 & if\ x \geq 0 \end{cases}$$

- Drawbacks:
  - The weights are FIXED. This means that we are unable to model learning in the general sense. Recall that learning in synapses means that their weights are either potentiated or depressed (LTP or LTD respectively) based on some activity. This model fails to describe such a phenomenon and hence an upgraded or alternate form is needed.

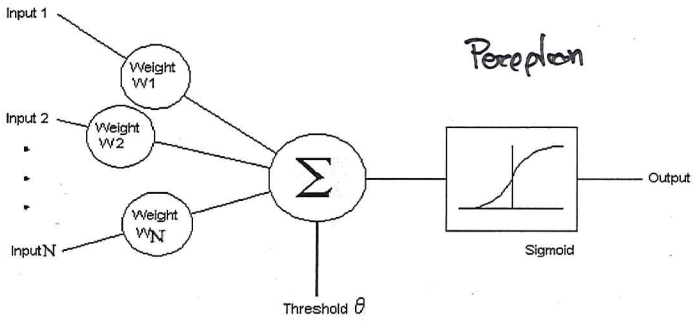
IV. The Perceptron Learning Algorithm:

- For this reason, Rosenblatt proposed the perceptron models in 1958 which has adjustable weights according to the perceptron learning algorithm.
- This is the mathematical model of the perceptron, where the 'sigmoid' block here replaces the θ(x) function in the previous section. This function is usually referred to as the activation

function, which basically gives an indication, a signal, or a threshold, to the perceptron whether to fire or not. Why do we sometimes use a step-function {0,1} and at other times a sigmoid function? Well, the sigmoid function can be very useful in applications where training a large network is involved. This is because when we talk about the error back propagation, we will see why it is important to have a differentiable function as an activation function. The sigmoid works perfectly because of its smooth ascent from the limits (-1 to 1). The step function on the other hand produces an abrupt ascent making the derivative none other than the delta function, which probably does not work for the purposes of these networks ~~(is this the case? Not really sure tbh)~~.

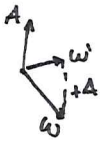
step

sigmoid



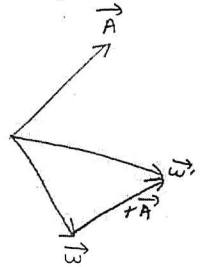
- We established in Section III that the output of a McCulloch-Pitt's neuron is the dot product of the input vector and the weight vector added to the bias. θ(x) is referred to as the activation function, which we'll return to later when we talk about Hopfield networks and the error back propagation algorithm. The important part here to note is that when we're talking about one perceptron, we can easily apply the following algorithm in order to *train* the unit, or cause it to learn a desired pattern:
  1. We start with an arbitrary set of weights.
  2. Compute the output for the training data given, using the weights we chose.
  3. If the output we get corresponds to the desired output, we proceed to the next sample in the training data set.
  4. If the output does not correspond to the desired output, this means we have one of two cases:
     a. Either the sum that we get is < 0 but it should be >= 0. This means that the angle between the input vector **A** and the weight vector **W** is greater than 90, which caused the cosine to yield a negative number when we took the dot product of the two vectors. To make it smaller, we ADD vector **A** to vector **W** and repeat steps 1-4.

$< \quad \geq$



$\omega_i \mathrel{+}= \alpha(d - y)x_i$ (d: desired, y: actual result)

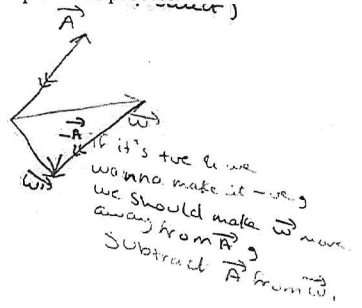
$\omega \mathrel{+}= \frac{1}{2}(1 - (-1))A$



b. Or, the sum that we get is >= 0 but it should be < 0. This means that the angle between vector A and vector W is less than 90, and in order to increase it we SUBTRACT vector **A** from vector **W** and repeat steps 1-4. The vector diagram below should help explain this process.

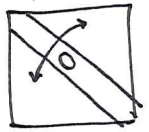
$\geq \quad <$

$\omega \mathrel{+}= \frac{1}{2}(-1 - 1)$

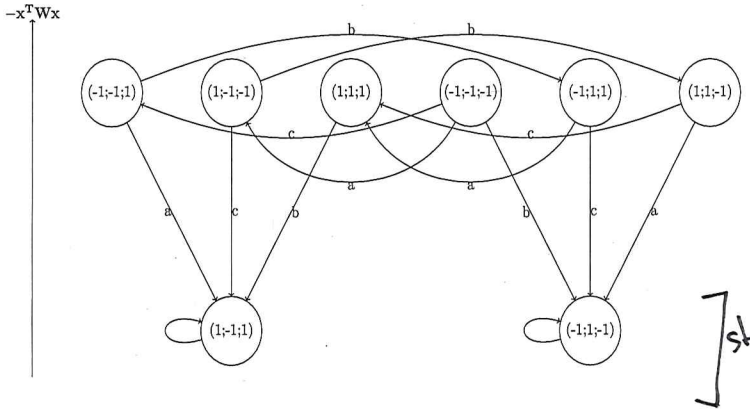


V. Hopfield Networks:

- The previous section was dealing with an individual unit ~~tl THINK, I'm not really sure, this is what I understood after a terrible struggle with this part~~.
- Enter Hopfield and his network of interacting perceptrons and this is where things start getting really interesting.
- Hopfield showed that for a network with the following properties, u always reach a stable state using the Lyapunov function or the energy analysis:
  - No self weights are allowed: This means that for any given unit, you cannot have its output connected to its input to avoid complexities that arise from the formation of feedback loops.
  - The network must have symmetric weights (symmetric means that $W_{ij} = W_{ji}$. In English, this means that the weight from the ith to the jth element is the exactly the



same as from the jth to the ith element. Otherwise, the system won't converge to a stable state).
    - The weight matrix for the system must have a zero diagonal. Again, if this is not the case, the system does not converge to a stable state. The exact mathematical proof of this completely eludes me ☹ Sorry!
- Now when you have a network of perceptrons connected together, training them becomes more complicated than before.
- **How do I asynchronously update a Hopfield NW? (info retrieval??)**
    1. For the number of inputs you have, calculate all possible combinations of input vectors: the number of possible combinations = 2^n, 2 because your input is binary and n represents the number of possible inputs.
    2. Calculate the output according to the perceptron/network learning rule that you have and according to the weights that are given (if you already have the weights, then this is probably information retrieval phase, otherwise ur probably trying to find the weights that will enforce the learning of a specific pattern). Remember **Y = A** dot **W!**
    3. If the network follows the conditions highlighted above, then this should converge to some stable states, and hence you should find some states that always give rise to themselves. These are your stable states!
    4. I followed the example that we had in the exercises, and to transition from one state to the next, apparently they only had a one bit change, something similar to grey encoding, or in Finite Automata when you transition from one state to the next you can only do so by changing a single letter/digit. I'm sorry I can't explain this very well, but this is the diagram they used in the solution:



- So for example, the get from one state (-1,-1,-1) to the stable state (-1,1,-1) (the one that self loops, or the dungeon state, because you can never leave it once you're there) by only changing the *b* input from -1 to 1. This applies to ALL states. All the transitions are done by changing only one variable.
- **How do I synchronously update the Hopfield NW?**
    - No idea whatsoever ☹

VI. Error Back Propagation:

- Previously, we were probing the network using the input to make it spit out what it had already stored.
- Now suppose we want to train the network to store something, or to recognize some patterns with a minimum error rate. What we do is we resort to the error back propagation simply defined as the derivative/ gradient of the error E:

$$E = \sum_i \frac{1}{2} \|y(x^i) - d^i\|^2$$

- This is sometimes called the mean square error and has the following advantages as used in this context:
    - You always get a "+ve" error every time there is an error.
    - Amplifies large numbers and suppresses small numbers.
    - So the math works out in your favour ☺
- Then what you do is you take the partial derivative of this guy (the error E) with respect to weights and then you'll notice that there is a term that is always there (called the delta term or the error term). (Please refer to the solution of the exercise on this part for more detail).
- So you probably calculate the delta function once beginning at the last functional block nearest the output (the highest unit) and then you keep computing the chain rule derivative all the way down the computational blocks until you reach the weight that you were originally differentiating with respect to in the lowest unit (the one closest to the input). This is why it is called error back propagation.
- Remember the sigmoid we introduced in the activation function? This is where it becomes useful! Because we are going backwards and differentiating as we're moving along, some neurons could be connected to others, so we end up with multiple activation functions that need to be differentiated. Please refer to the solution of the exercise on that part for more detailed explanation.

VII. Population Codes:

- If each neuron represents movement in its preferred direction (or orientation, where orientation does NOT mean direction of motion), and the vector sum of all the neurons in the

population is calculated, then the sum points to the overall direction (or orientation) of the stimulus.

- Can also be referred to as population vector coding.
- An important feature of this is a tuning curve, which takes the shape of a Gaussian curve: maximum firing (the peak) occurs when the stimulus direction is closest to the preferred direction of the cell.
- This is all I was able to find about this topic! Sorry ☹

- **Short-term plasticity:** last in the order of ms or minutes.
  - Facilitation
  - Post-tetanic potentiation (PTP) (see Saee's notes on this).
- **Long-term plasticity**, of which the two most prominent forms are:
  - Long-term potentiation (LTP)
  - Long-term depression (LTD)
- **LTP: lasts for a few hours or more**
  - A long-lasting increase in the amplitude of a synaptic response following brief, high frequency activity of a synapse.
  - It could also be defined as an enduring, activity-dependent increase in synaptic efficacy.
  - LTP has two phases:
    - Induction: occurs during and shortly after hi-frequency stimulation used to initiate LTP. It consists of all the steps and mechanisms that lead to the long-lasting changes that are associated with LTP.
    - Maintenance: follows induction, and is the phase during which the change in synaptic efficacy is actually expressed.
  - The mechanisms of LTP may be different at different synapses and hence their timings may differ.
  - In general, we can measure LTP by recording the amplitude of the synaptic response before and after the period of hi-freq stimulation.
- **Neuromodulation:**
  - LTP can modulated by various neurotransmitters such as:
    - Norepinephrine (NO)
    - Acetylcholine (ACh)
    - Serotonin
    - Dopamine (DA)
    - Adenosine
    - Some neuroactive peptides
  - This neuromodulation is different for different synapses:
    - In the hippocampus, NO enhances LTP at perforant path synapses in the absence of hi-freq stimulation, enhances LTP at mossy fiber synapses with hi-freq stimulation, and has no effect on LTP at Schaffer collateral synapses.
- **Characteristics of LTP:**
  - *Input specificity*: This means that the fibers (synapses) that are given the high frequency stimulation are the only ones that get potentiated. Another term for this is *homosynaptic*. In some rare circumstances, LTP can exhibit *heterosynapticity* in which one stimulated pathway causes the potentiation of another non-stimulated pathway. However, LTP is mostly homosynaptic.
  - *Cooperativity*: for LTP to be induced, a certain threshold must be surpassed. For this to occur, a minimum number of input fibres must be activated in order to induce LTP. This means that the stimulus intensity must exceed a certain threshold. However, if the

stimulus level becomes too high, a maximum level of potentiation is achieved such that no further LTP can be induced. This is called LTP *saturation*.

- *Associativity*: This can be thought of as the molecular analog of classical conditioning such that LTP could be induced in a weaker contralateral pathway only if its stimulation was paired with stimulation of the stronger ipsilateral pathway. The weak pathway corresponds to the conditioned stimulus, while the strong pathway can be thought of as the analog of the unconditioned stimulus. **Note:** associativity implies cooperativity though the converse is not true: cooperativity does not necessarily imply associativity.
- **DIAGRAM COPIED FROM SAEE'S NOTES:**

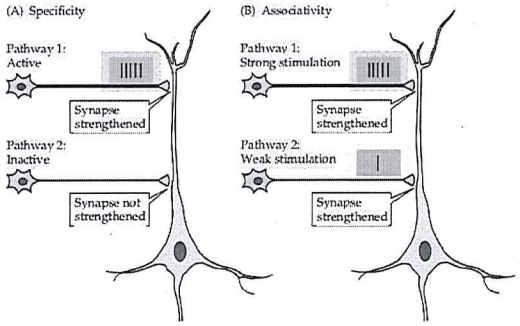
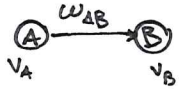


Figure 24.8 Properties of LTP at a CA1 pyramidal neuron receiving synaptic inputs from two independent sets of Schaffer collateral axons. (A) Strong activity initiates LTP at active synapses (pathway 1) without initiating LTP at nearby inactive synapses (pathway 2). (B) Weak stimulation of pathway 2 alone does not trigger LTP. However, when the same weak stimulus to pathway 2 is activated together with strong stimulation of pathway 1, both sets of synapses are strengthened.

- **Hebbian Rule for Synaptic Plasticity:**
  - We define synaptic efficacy as a synaptic weight W_{AB}, where W_{AB} represents the weight or synaptic strength from neuron A to B, and V_A and V_B represent the firing rates of neurons A and B respectively.
  - Hence the change in the synaptic weight ΔW_{AB} is:

$$\Delta W_{AB} = F(V_A, V_B)$$

where F is some function of V_A and V_B



  - The simplest thing is to set F as the multiplication of V_A and V_B with some multiplicative constant k:

$$\Delta W_{AB} = k(V_A \cdot V_B)$$

  - Problems that arise with this model are:
    - Only weight increase (potentiation) is modeled. Does not model depression.
    - Leads to instability due to the positive feedback loop and even in this case does not put a limit on the max weight value to model the LTP saturation we talked about earlier.
    - To solve this problem, other rules were proposed such as the BCM rule and Oja's rule.

- **So how does LTP work at the cellular level?**
  - There are two forms of mechanisms:
    - Those that require the activation of NMDA receptors (Ca influx through NMDA receptors)
    - Those that do not (Ca influx through voltage-gated Ca channels).

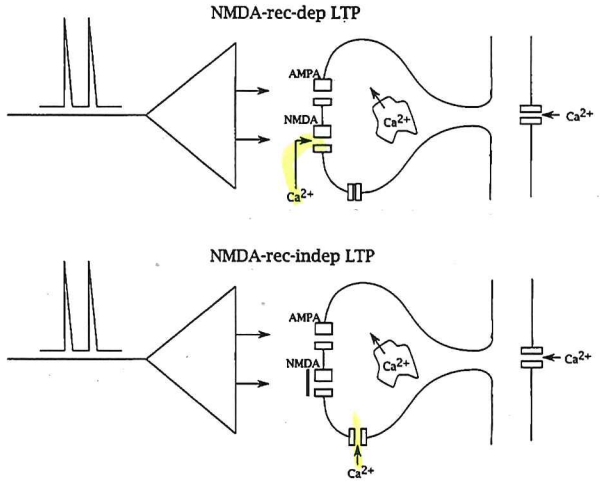


Figure 15.12 Induction mechanisms for NMDA and non-NMDA LTP. For NMDA-rec-dep LTP, Ca^{2+} entry through NMDA receptors during the HFS is believed to initiate LTP. For NMDA-rec-indep LTP, Ca^{2+} may enter through voltage-gated Ca^{2+} channels to initiate LTP. Ca^{2+} may also be released from intracellular stores.

  - We focus on those that do because those are more intensely studied.
  - **COPIED FROM SAEE's NOTES:** "Ca2+ induces LTP by activating complicated signal transduction cascades that include protein kinases in the postsynaptic neuron. At least two Ca2+-activated protein kinases have been implicated in LTP induction: Ca2+/calmodulin-dependent protein kinase (CaMKII) and protein kinase C (PKC). CaMKII is also important in inhibiting LTP. This leads to a complicated cascade that results in the insertion of more AMPA receptors into the membrane. AMPA receptors are what lead to the expression or maintainance of LTP. LTP is triggered by Ca+2 actions on the post-synaptic neuron, which then must act in a retrograde fasion (most likely through NO) to affect the pre-synaptic side. In the case of glutamatergic synapse, the NMDAR can act as a coincidence detector for pre and post synaptic firing, traasmitting backpropagating action potentials and depolarization from other synapses. In the case of strong NMDAR activation, you

get potentiation, and in the case of weak NMDAR activation, you get depression. Low frequency stimulation, for this reason, results in synaptic depression." **THANK YOU SAEE!**

- **LTD:**
  - There exists good evidence that smaller increases in postsynaptic Ca levels leads to LTD while larger increases lead to LTP.
  - LTD has been referred to as anti-Hebb bec it is induced under non-Hebbian conditions. In other words, it is the complete opposite of the Hebbian rule, or the Hebbian rule fails to account for it.
  - Without LTD, we reach LTP saturation and we cannot get more learning. For this reason we need to introduce the LTD learning rules, or modify the existing Hebbian rule.
  - The two modified rules that I read in this book:
    - **The covariance rule:**
      - $\Delta W_{AB} = k[(V_A - \overline{V}_A)(V_B - \overline{V}_B)],$
      - ΔW_{AB} represents the change in synaptic weight, V_A and V_B represent the activities of the pre- and postsynaptic neurons, respectively, and $\overline{V}_A$ and $\overline{V}_B$ represent the average values of the activities or firing rates of neurons A and B. From this equation, if the activities of A and are correlated in time, then the change in weight will be positive, while if they are negatively correlated, the weight change will be negative. If there is no correlation, then there will be no change.
    - **The BCM rule:**
      - Named after its creators: Bienenstock, Cooper, and Munro, it is rather similar to the previous rule yet differs in the following aspects:
        - The relationship is nonlinear.
        - There can be a threshold for potentiation and another for depression.
        - These thresholds vary as function of the average activity of the post-synaptic neuron: the higher the average background activity of the postsynaptic neuron, the higher the threshold for enhancing synaptic efficacy. Conversely, the lower the average background activity, the lower the threshold for an LTP-like process.

          $\Delta W_{AB} = \phi(c_B, \overline{c}_B) d_B$

          and
        - $\theta_M = \overline{c}^2$
        - where Φ is the nonlinear function relating changes in synaptic weigh resulting from the correlated activity of neurons A and B (c_B) and the average correlated activity ($\overline{c}_B$); d_B is a local variable for synapse *AB;* and θ_M is the modification threshold for LTP vs. LTD.

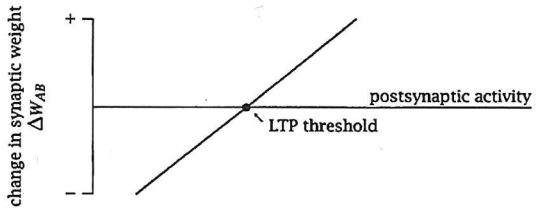


Figure 15.14 Plot of covariance rule. The abscissa represents the postsynaptic activity that is correlated with, or in response to, presynaptic activity.

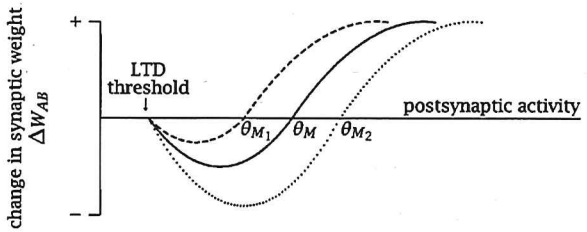


Figure 15.15 Sliding modification threshold rule for synaptic plasticity. The higher the average activity levels in the postsynaptic neuron, the more activity that is necessary to induce LTP (i.e., the larger the θ_M).

(1/3)

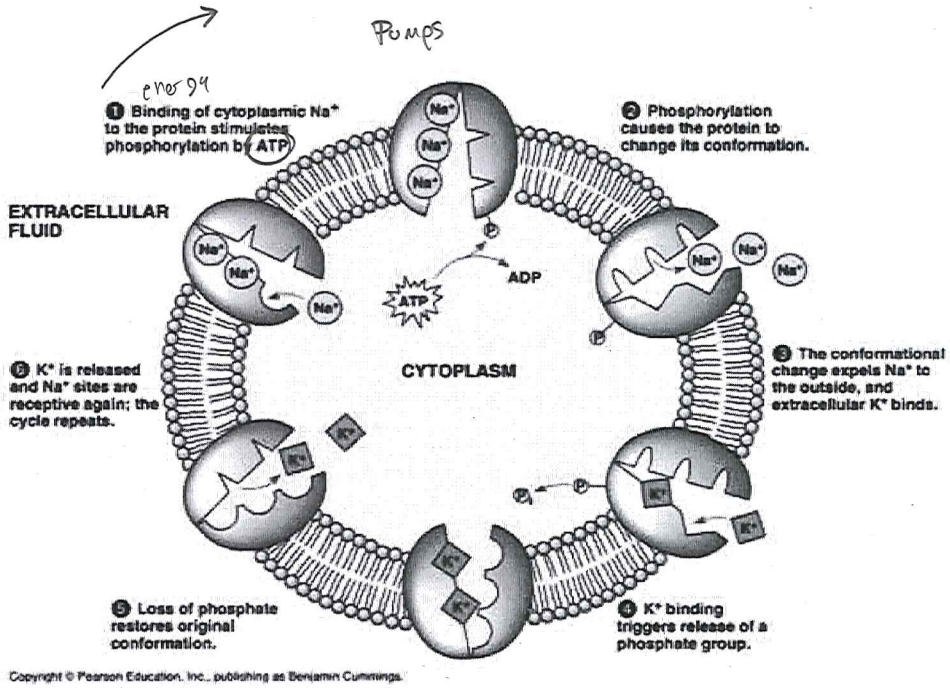
Summary of Rodney's Lectures

NS og AP

- Remember! Current convention is defined as positive from intracellular (top of the circuit) to extracellular (bottom of the circuit).
- Membrane potential Vm: the voltage difference across a cell membrane:

$$V_m = V_{in} - V_{out}$$

- Resting potential: the potential across the cell membrane when the cell is at **rest**. So in other words, it is a special case of the membrane potential Vm under specific circumstances. It is determined by the reversal potential of the ion whose channels dominate the membrane conductance (because they are open for ex and all other channels are closed) (I THINK).
- A typical neuron has a resting potential of about -70mV.
- There are two types of currents that we are interested in:
  - An inward current: corresponds to a positively charged ion such as Na^+ entering the cell. Since the sodium-potassium pumps have already established a higher gradient of sodium ions outside the cell and a higher gradient of potassium ions inside the cell, then sodium ions diffuse into the cell. This would increase the value of V_{in} making Vm approach a higher voltage (approach zero volts from the -70mV resting potential). This is referred to as **DEPOLARIZATION**.
  - An outward current that corresponds to either:
    - A positive ion exiting the cell (such as potassium)
    - A negative ion entering the cell (such as chloride)
    - These would decrease the value of Vin hence making Vm more negative, resulting in **HYPERPOLARIZATION**.
- Schematic of the sodium-potassium pump that establishes the gradients that we need in order to obtain an inward or outward current:


EXTRACELLULAR FLUID
CYTOPLASM
1 Binding of cytoplasmic Na+ to the protein stimulates phosphorylation by ATP.
2 Phosphorylation causes the protein to change its conformation.
3 The conformational change expels Na+ to the outside, and extracellular K+ binds.
4 K+ binding triggers release of a phosphate group.
5 Loss of phosphate restores original conformation.
6 K+ is released and Na+ sites are receptive again; the cycle repeats.
ATP
ADP
Na+
K+
P
Pi
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- There are two types of channel proteins in the lipid bilayer:
  - Gated-channels: open based on specific conditions and the permeability of the membrane to a specific ion depends on the number of open ion-channels:
    - Voltage-gated
    - Ligand-gated
  - Non-gated: always open: responsible for the leakage current term.

- Since most gated-ion channels are closed and non-gated are open during rest, the non-gated ion channels are thus responsible for establishing the resting potential.
- An important concept is that of the reversal potential: The reversal potential of an ion is the membrane voltage at which there is NO NET flow of that ion across the membrane of the cell.
- The reversal potential is sometimes referred to as the Nernst Potential and can be calculated from the Nernst equation. This is what corresponds to the E_K and E_{Na} batteries that we place in our electrical model.
- http://www.youtube.com/watch?v=LXdTg9jZYvs (action potential video)
- The resting potential is the potential at which there is a balance between the influx of Na and Cl-, and the efflux of K.

- At rest, many more K and Cl- channels are open than Na channels, hence the cell's resting potential tends towards that of K and Cl- Nernst potential.
- The Goldman-Hodgkin-Katz (GHK) eqn is an expression for how the resting potential depends on the intra and extracellular concentrations of ions and the permeabilities of the membrane to those ions.

The Nernst Equation:

- We consider a membrane that is permeable to only one type of ion.
- If the membrane is permeable to only one type of ion, then the Nernst potential is the resting potential at which the electrical (drift) and chemical (diffusion) driving forces balance out.
- Fick's law of diffusion:

$$J_{diff} = -D\frac{\partial[C]}{\partial x}$$

- This means that the diffusion flux is simply the diffusion constant D (cm^2/s) multiplied by the change in ionic concentration [C] ($molecules/cm^3$). The direction of flow is from hi concentration to lo concentration.
- A typical value for D for ions such as K, Na, and Cl is $2.5*10^{-6}$ cm^2/s.
- The electrical force is generated by the microscopic version of Ohm's law, or the drift flux:

$$J_{drift} = -\mu z[C]\frac{\partial V}{\partial x}$$

- $-\frac{\partial V}{\partial x}$ is the electric field E, measured in V/cm, z is the valence of the ion ($\pm1, \pm2...$), and μ is the mobility ($cm^2/(Vs)$). The higher the concentration, the greater the drift (makes sense).
- Hence the total flux is basically the sum of these driving forces:

$$J_{tot} = -D\frac{\partial[C]}{\partial x} - \mu z[C]\frac{\partial V}{\partial x}$$

- And replacing D by Einstein's relation we get:

$$J_{tot} = -\frac{\mu kT}{q}\frac{\partial[C]}{\partial x} - \mu z[C]\frac{\partial V}{\partial x}$$

where k is Boltzmann's constant (J/K), T is the absolute temperature, and q is the charge (C).

- We divide by Avogadro's number (number of molecules per mole) to obtain the molar form (much more convenient than expressing it in its molecular form), which will yield the flux per mole. Multiplying this by the valence and Faraday's constant gives the **current flux** (A/cm^2):

$$I = -\left(uRT\frac{\partial[C]}{\partial x} + uz^2F[C]\frac{\partial V}{\partial x}\right)$$

Notice here that we have a u instead of μ, which is the molar mobility (μ/N_A), where N_A is Avogadro's number.

- This is the Nernst-Planck Eqn. By setting this eqn to 0, we can solve for the equilibrium or resting potential (which is also called the Nernst potential) of a specific ion. This is called the Nernst Equation:

$$V_{eq} = V_{in} - V_{out} = -\frac{RT}{zF}\ln\frac{[C]_{in}}{[C]_{out}}$$

The GHK Equation:

- A generalization to the Nernst eqn, such that we consider a membrane that is permeable to more than one type of ion.
- This equation determines the resting potential at which the electrical (drift) and chemical forces (diffusion) generated by such ions balance each other.
- They used the following assumptions to derive their equation (a.k.a. the constant field equation):
  - The electric field across the lipid membrane is constant.
  - The Nernst-Planck Equation holds within the membrane.
  - The ions move independently.
- Since the Nernst Equation describes the movement of charged ions in an aqueous medium, it does not accurately describe the behavior of the gated channels within the membrane. For this reason, we also introduce the *'ionic permeability'* term to describe the rate at which ions cross the membrane.
- Because the mobility of ions across the membrane differs from their mobility within an aqueous medium, we need to change the term μ with a more suitable one to describe the mobility across the membrane. Hence, we introduce the term u^*. Moreover, we need to introduce the factor β, which is the ratio of ion solubility within the membrane to the ion solubility in the aqueous solution. We end up with the following equation:

$$I = -u^*z^2F\beta[C]\frac{V_M}{l} - u^*zRT\beta\frac{d[C]}{dx}, \quad 0 < x < l$$

- Ok, so this is a 1st order ODE with 2 boundary conditions $[C](0) = [C]_{in}$, and $[C](l) = [C]_{out}$. It can be shown (no idea how) that after some mathematical derivations I is equivalent to the following:

$$I = \frac{u^*z^2FV_M\beta}{l}\left(\frac{[C]_{out}e^{-\xi} - [C]_{in}}{e^{-\xi} - 1}\right), \quad where\ \xi = \frac{zV_MF}{RT}$$

- Now we insert the permeability term (cm/s). (The reason why I include this vast derivation is bec it is not in the lectures, so I thought it might

make things a bit clearer...or maybe not :s). The permeability is defined as $\frac{\beta D^*}{l}$ and if we substitute D* with u*RT, we can get the following monster:

$$I = PzF\xi \left(\frac{[C]_{out}e^{-\xi} - [C]_{in}}{e^{-\xi} - 1}\right)$$

- Maybe it's not really a monster, it looks a lot better than before :p. Anyway, this still does not solve the problem because this is the current due to a single ionic species ☹ However, this is where the third assumption becomes very useful: since we assumed that the ions do not interact, then we can simply state that the total current is the sum of the currents due to the individual ionic components!
- At equilibrium, $I = I_K + I_{Na} + I_{Cl} = 0$. The potential at which this happens is described as follows:

$$V_M = \frac{RT}{F} \ln\left(\frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^-]_{in}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{out}}\right)$$

- How or why we get this eqn, I have no clue ☹

The Equivalent Circuit Model:

- So far so good. Let's complicate stuff a bit. So far we've limited our discussion to the steady state behavior of membranes and ionic fluxes: i.e. we do not account for:
  - Changing membrane conductances
  - Nor do we account for (or for that matter can mathematically describe) action potentials.
- Enter Hodgkin and Huxley and their giant squid experiment, which basically paves the way for modeling the conductances as functions of both the **changing membrane voltage** and **time**.
- But first.... We need to understand how we can model a simple cell membrane using basic electrical components and account for basic phenomena such as signal decay through a cable before we can attempt to derive the H-H model.
- Here is the model we use:

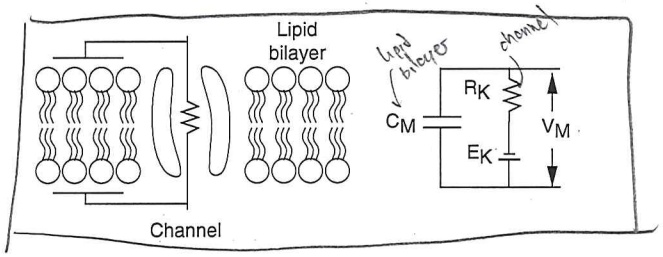


Fig. 1.2 The cell membrane showing the insulating lipid bilayer and a K^+ channel, which allows current to flow. The equivalent electrical circuit is shown on the *right*

- Remember this diagram and you're done!

  - Channels are modeled as Resistors (R) or conductances (G) which is the reciprocal of R. This makes sense because if a channel is closed, the resistance value increases (or the conductance decreases). This is because it impedes the flow of ions from one side of the membrane to the other.
  - The lipid bilayer can be modeled as a capacitance because you can store charge on its surface. In other words, it behaves like a dielectric (a capacitor). The charge on the surface of the membrane can be modeled as follows, where C_M is the membrane capacitance and V_M is the membrane potential:

$$q = C_M V_M$$

  - E_K in this diagram denotes the Nernst (reversal/equilibrium) potential for potassium, and is modeled by the battery or voltage source.

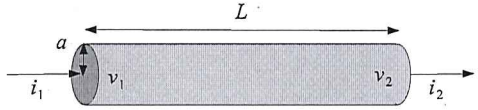
The Cable Equation:

- Ok, so now we need to derive the cable equation. This is because from electromagnetic theory, current decays if transported in a cable/transmission line. In electrical engineering, they use repeaters to solve this problem. In biology, axons use action potentials. For example, the C. elegans does not have action potentials because it does not *need* them. This is because the length of its longest axon does not surpass the threshold for decaying the signal (the space constant).
- The books explain this part in a rather complex and unpleasant way, so I will resort to the derivation done in class:

The membrane potential along a neuronal cable is expressed as a function of a single longitudinal spatial coordinate x and time, $V(x, t)$.

Current flows within a neuron due to voltage gradients.

Currents flowing in the direction of increasing x are defined to be positive.



specific membrane parameters (independent of geometry)

$R_m = 10\,k\,\Omega\cdot cm^2$, $R_a = 100\,\Omega\cdot cm$, $Cm = 1\mu F/cm^2$

axial resistance $r_a = \frac{R_a L}{\pi a^2}$

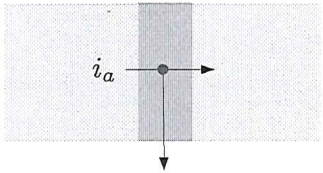
membrane resistance $r_m = \frac{R_m}{2\pi a L}$

membrane capacitance $c_m = C_m 2\pi a L$

r_a, r_m, c_m are cylinder (geometry) dependent parameters

$$\frac{\partial v}{\partial x} = -r_a i_a \qquad \frac{\partial^2 v}{\partial x^2} = -r_a \frac{\partial i_a}{\partial x} = r_a i_m$$

$$\frac{\partial i_a}{\partial x} = -i_m \qquad \frac{1}{r_a}\frac{\partial^2 v}{\partial x^2} = i_m$$



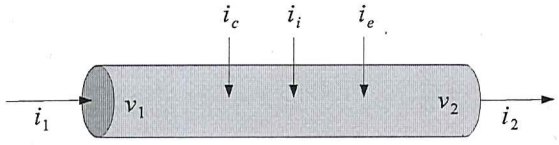
$$\frac{1}{r_a}\frac{\partial^2 v}{\partial x^2} = c_m \frac{\partial v}{\partial t} + \frac{v}{r_m}$$

$$\lambda^2 \frac{\partial^2 v}{\partial x^2} = \tau \frac{\partial v}{\partial t} + v$$

$$i_m = i_c + i_i + i_e$$

$$i_m = i_c + i_i = c_m \frac{\partial v}{\partial t} + \frac{v}{r_m}$$

$$\lambda = \sqrt{\frac{r_m}{r_a}} = \sqrt{\frac{aR_m}{2R_a}} \approx 0.6mm$$



To cut a long story short,
the 'cable equation' becomes finally...

$$\lambda^2 \frac{\partial^2 v}{\partial x^2} = \tau \frac{\partial v}{\partial t} + v$$

$$\lambda = \sqrt{\frac{r_m}{r_a}} = \sqrt{\frac{aR_m}{2R_a}} \approx 0.6mm$$

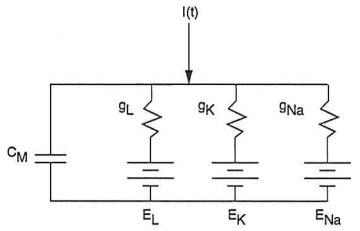
$$\frac{\partial v(x)}{\partial t}=0, \quad v(x)=\frac{r_\lambda i_e}{2} e^{\frac{-x}{\lambda}}$$

Hodgkin and Huxley's Action Potential Model:

- From the previous "slide", we've seen that the voltage decays with the space constant lambda ($e^{-x/lambda}$ term). This would cause a problem for the signal to travel across axons. Hence we have action potentials. In a simple circuit consisting only of Na and K conductances, this is the equation:

$$c_M \frac{dV}{dt} = -g_{Na}(V - E_{Na}) - g_K(V - E_K) - g_L(V - E_L).$$

- And this is the ckt:



- When H&H performed their voltage clamp experiments on the squid giant axon, they got a curve similar to the one shown below:

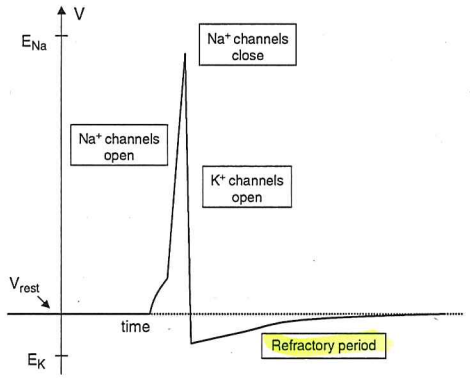


Fig. 1.7 The action potential. During the upstroke, Na^+ channels open and the membrane potential approaches the Na^+ Nernst potential. During the downstroke, Na^+ channels are closed, K^+ channels are open, and the membrane potential approaches the K^+ Nernst potential

- This led them to hypothesize (and they were right) that there were two major components that contributed to this action potential: the sodium and potassium currents.
- This is the basic mechanism of how the action potential works:

At rest, most of the Na channels are closed, so the membrane potential is deter-

mined primarily by the K Nernst potential. If the cell is depolarized above some threshold, then Na channels open and this further depolarizes the cell. This allows even more Na channels to open, allowing more Na ions to enter the cell and forcing the cell toward the Na Nernst potential. This is the upstroke of the action potential. The Na channel is transient, so even when they are depolarized, the Na channels eventually shut down. In the meantime, the depolarization opens K channels and K ions exit the cell. This hyperpolarizes the cell as the membrane potential moves toward the K equilibrium potential. Until the voltage-gated K channels close up again, the membrane is refractory. During this time, pumps exchange excess Na ions inside the cell with excess K ions outside the cell.

- This is how they quantified this phenomenon:
  - First of all, the K and Na channels are voltage gated. (Remember at the very first page we established that there are two types of channels: ligand-gated channels and voltage-gated channels).
  - To get this different dynamic behavior, the gating mechanism for both the Na and the K channels must therefore be different.
  - Let's first consider this model:

$$C \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}} O,$$

  - Alpha and Beta represent voltage-dependent rate constants. This means that they determine the speed at which the gates change from one state to the other. *C* stands for the *closed* state, while *O* stands for the *open* state. So in other words, we want to represent the rate at which the gates change state from open to closed and vice versa.
  - If we let *m* represent the fraction of open gates (where each channel can have multiple gates), then it follows that 1-m is the fraction of closed gates; and the opening rate of the gates is simply the time it takes the closed gates to open minus the time it takes the open gates to close:

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha(V)(1-m) - \beta(V)m = (m_\infty(V) - m)/\tau(V)$$

  - Where

$$m_\infty(V) = \frac{\alpha(V)}{\alpha(V)+\beta(V)} \quad \text{and} \quad \tau(V) = \frac{1}{\alpha(V)+\beta(V)}.$$

  - Solving this we get:

$$m(t) = m_\infty(V) + (m(0) - m_\infty(V))\mathrm{e}^{-t/\tau(V)}.$$

  - This means that: The number of open channels approaches a steady state depending on the time constant Tau(V), which in turn depends on the membrane voltage.
- What does all of this have to do with H&H? Well, everything! It shows that the gates of a channel are governed by a time constant, which is in itself a function of the membrane voltage.
- Moreover, from the voltage clamp experiments, we get the following diagram:

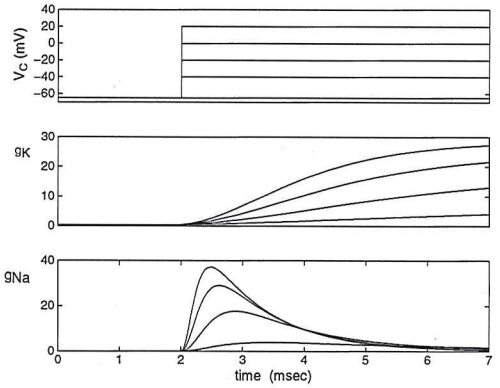


Fig. 1.9 Numerically computed voltage-clamp experiment. The membrane potential is stepped to different values and the resulting K^+ and Na^+ conductances are computed

- Note than g_{Na} turns on more rapidly that g_K. Moreover, the Na channels begin to close before the depolarization is turned off, whereas the K channels remain open as long as the membrane is depolarized. This suggests the Na channel can exist in three states: **resting**, **activated**, and **inactivated.**
- This is explained very nicely in the diagram below.

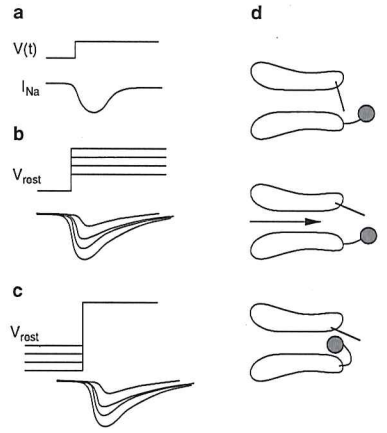


Fig. 1.10 The Hodgkin–Huxley Na^+ channel. (**a–c**) Voltage-clamp dynamics. (**d**) Physical model of the channel. If the voltage step is small (**d**, *top*) then the Na^+ channel's activation gate (*line*) is closed but the inactivation gate (*ball*) is open. At intermediate steps (**d**, *middle*), both gates are partially open. For large steps (**d**, *bottom*), the activation gate is open and the inactivation gate is closed

- n^4 means that we need all 4 latches (gates of the channel) to be open in order

for the K+ ions to flow. From probability theory, if I want all the four gates to be open, I multiply them together (boolean AND). This can be drawn from the analogy of the Na channel which has a ball and a line that need to be both open simultaneously to allow the Na ions to flow.

- This is the equation they came up with:

$$g_{\mathrm{K}} = \bar{g}_{\mathrm{K}} n^4 \quad \text{and} \quad g_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} m^3 h,$$

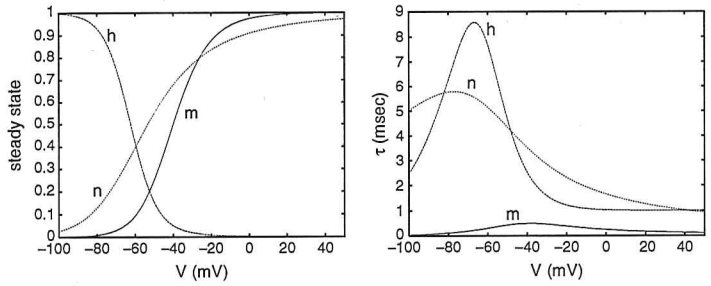
- where (gK)bar and (gNa)bar are maximum conductances and n, m, and h are gating variables that take values between 0 and 1. Hence, n^4 represents the probability that a K channel is open: the K channel has four independent components, all of which are identical. The probability that the sodium activation gate is open is m^3 and **the probability that the sodium inactivation gate is open is h**. Each of the gating variables satisfies a first-order differential equation of the form (1.34). That is, they satisfy equations of the form:

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n = (n_\infty(V) - n)/\tau_n(V),$$
$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m = (m_\infty(V) - m)/\tau_m(V),$$
$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h = (h_\infty(V) - h)/\tau_h(V).$$

If $X = n, m,$ or h, then

$$X_\infty(V) = \frac{\alpha_X(V)}{\alpha_X(V) + \beta_X(V)} \quad \text{and} \quad \tau_X(V) = \frac{1}{\alpha_X(V) + \beta_X(V)}. \qquad (1.42)$$

- This is why we used the C→ O diagram above with the alpha and beta derivations to begin with.
- Thus these are the activation curves for the n, m, and h variables (the smaller the tau, the faster it is, bec tau represents the delay):



- And this becomes the most imp diagram of all:

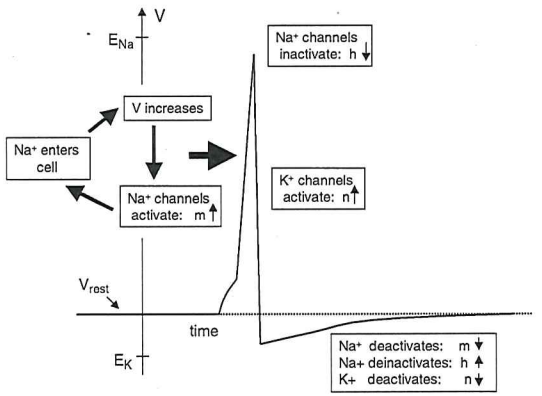


Fig. 1.15 Mechanisms underlying the action potential

Synapses:

- An inhibitory synapse is one where the reversal (Nernst) potential is more negative (hyperpolarized) than the resting potential.
- An excitatory synapse is one where the reversal (Nernst) potential (E_K, E_{Na}) is more positive (less negative) (more depolarized) than the resting potential.